EFFECT OF PYRITINOL OVER SEQUELAE OF CRANIOCEREBRAL INJURIES: A CONTROLLED COMPARATIVE STUDY

THESIS FOR

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C E R T I F I C A T E

Certified that the work entitled "EFFECT OF PYRITINOL OVER SEQUELAE OF CRANIOCEREBRAL INJURIES : A CONTROLLED COMPARATIVE STUDY", has been carried out by DR. RAJEEV KUMAR SHARMA, under my constant supervision and guidance. The results and observations were checked and verified by me from time to time.

This work fulfils the basic ordinances governing the submission of thesis for M.S., laid down by Bundelkhand University.

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C E R T I F I C A T E

Certified that the work entitled "EFFECT OF PYRITINOL OVER SEQUELAE OF CRANIOCEREBRAL INJURIES : A CONTROLLED COMPARATIVE STUDY", has been carried out by DR. RAJEEV KUMAR SHARMA himself in the department of Surgery, M.L.B. Medical College, Jhansi.

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Lastly I am obliged to the greatest extent to those unfortunate injured patients who became the subject of this work.

Dated : 8.8.91.

(Rajeev Kumar Sharma)

CONTENTS

INTRODUCTION

INTRODUCTION

It is well known to all that accidental injuries are the leading cause of morbidity and mortality all over the world and the leading cause of death in individuals between 1 and 44 years of age. Head injuries are present in more than 50 percent of trauma related deaths. In most countries primary and continuing care of patients sustaining a head injury is the responsibility of general surgeons rather than neurosurgeons. Despite the expansion of neurosurgical services this situation is likely to continue and therefore a general surgeon requires a knowledge of principles and practice in this field. Since most of the patients do not require any neurosurgery, the major steps in the care of such patients are medical, diagnostic and nursing, and it is these steps which will determine the outcome far more frequently than any surgical manoevers.

The final neurological status of the patient, who has sustained brain trauma is the sum of irreversible damage acquired at the time of initial injury and the damage that is the consequence of secondary insults. At the time of initial injury one portion of brain may sustain irreversible damage from which it will recover over a period of months. Secondary insults that result

in worsening of patient's neurological deficits include :-

1. Systemic disorders as hypoxia or hypotension.
2. An expanding intracranial mass as subdural, epidural or rarely an intraparenchymal haematoma.
3. Sustained raised intracranial pressure.

Several forms of intervention have been proposed to enhance brain's normal repair process but little can be done about it, only swift recognition or prevention of these secondary insults offers the best chance of improving the prognosis of patients who have sustained a brain injury.

Patients with mild head injuries and brief loss of consciousness are often expected to make an uneventful recovery. In fact, these patients are found to have a surprising degree of post injury disability in the form of persistent headaches, memory deficits, and difficulties with activities of daily living that persist for months following the accident. Rimel, Giordani, and Barth(1981) reported that one third of patients who had sustained minor head injuries had not returned to gainful employment in 3 months following injury. Patients who have sustained mild head injuries but have a severe headache, lethargy or restlessness should be observed for 24 hours. If the patient shows any deterioration in neurological status or demonstrates any signs of a focal neurologicalesion on examination, CT scan should be performed. Patients who

have sustained a moderate head injury are likely to be lethargic, stuporous, or combative when they first regain consciousness. Ten to fifteen percent of patients entering the hospital with a moderate head injury are found to have a focal intracranial lesion. Nearly all patients who sustain injury of this degree suffer from persistent headaches, memory difficulties and difficulties of daily living for months following injury. Three months following a moderate head injury, two thirds of patients still do not return to their normal work.

A severe head injury is defined by a score of eight or less on Glasgow coma scale. Almost forty percent of patients sustaining a severe brain injury have a focal intracranial mass lesion. Signs of severe neurologic dysfunction, such as an abnormal motor response, abnormal oculocephalic reflexes or bilateral fixed pupils are common in this group of patients. Each of these brain stem reflexes can be demonstrated in approximately one third of severely injured patients and is associated with an increased mortality. Mortality has also been shown to be proportional to patients age. Other stated factors for poor outcome include presence of focal intracranial lesion or elevated intracranial pressure. Frequent neurological examination is necessary to detect any change in patient's neurological status.

There has long been felt a necessity for a drug which may affect recovery from craniocerebral injury in a positive way and minimize the sequele thereof. Chemicals such as magnesium pemoline, methyl phenidate and Pyritinol appeared on therapeutic scene. But of these PYRITINOL is the only drug that is still the subject of continuing research using modern and sophisticated methods. Substantiated reports of therapeutic efficacy of pyritinol have appeared as recently as 1980. So it is increasingly used in more than 70-80 countries around the world for the management of various neurological disorders, including sequele of brain trauma.

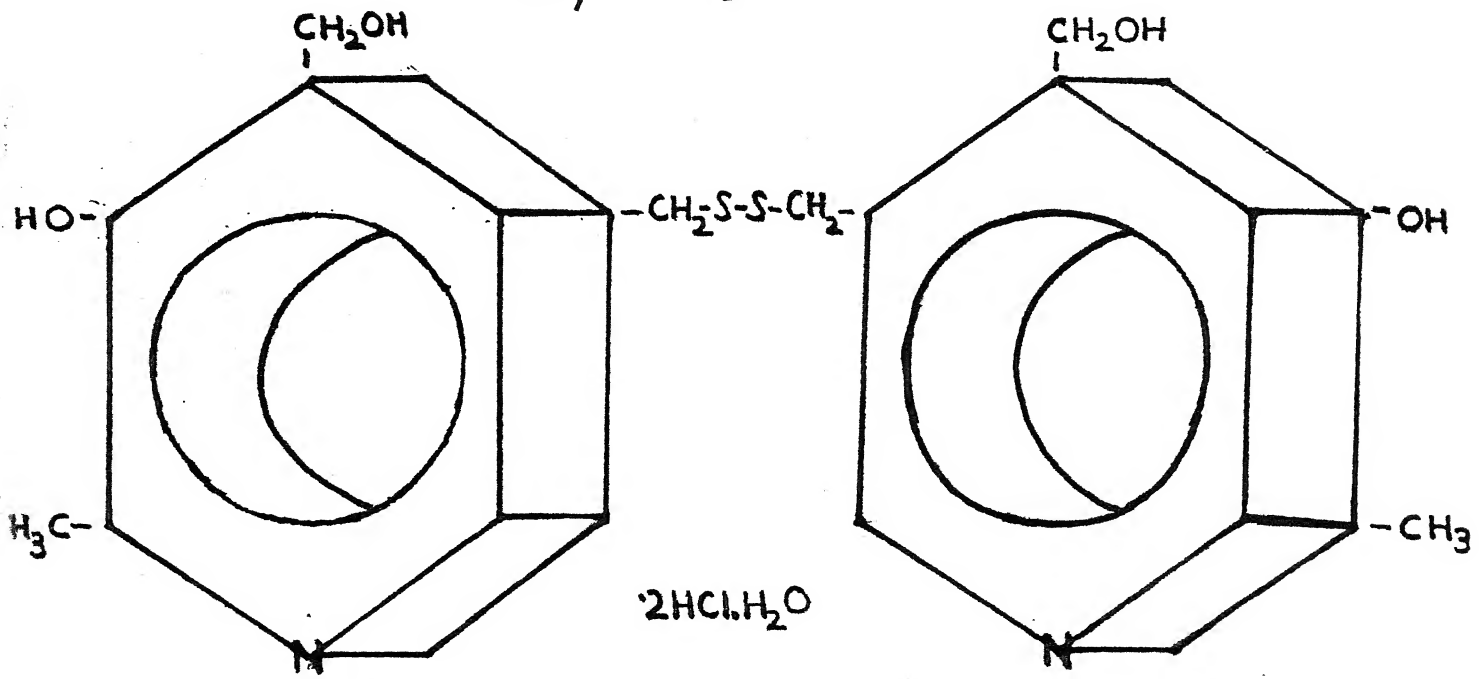
PYRITINOL was first introduced in India in 1967 and was considered a neurotropic compound. It is said to enhance glucose uptake and utilisation in neuronal cells and also to have some effect in G.A.B.A. metabolism in brain, stimulate nucleic acid metabolism and protein synthesis, activates cerebral cortex, limbic system and reticular activating system as well (last three effects are due to increased uptake of G.A.B.A.).

Molecule of PYRITINOL is derived from a combination of two molecules of pyridoxine (Vit. B_6). But the actions of the two compounds are dissimilar. The short chemical name is pyritinol or Pyrithioxine.

Pyritinol molecule was first synthesised in 1957 and subjected to detailed investigation which confirmed absence of any serious side effects or teratogenic effect in animals. Many people still challance its role in neurological abnormalities including sequele craniocerebral injuries and say that is empirical.

So the present study was undertaken to see and compare the development and duration of sequele of craniocerebral injury using pyritinol and comparing them with control group of similar patients.

ENCEPHABOL MOLECULE
(Pyritinol)



REVIEW OF LITERATURE

REVIEW OF LITERATURE

Head injuries are well known since time of evolution of man. At that time too people knew about their serious consequences.

Sushruta (1000 BC) believed that the head was the most important organ of human body for it was there that the life stayed and all the senses belonged. Later Hippocrates (460-377 BC) of Greece, who had been partly educated at school of Medicine Cnidia, where he was influenced by Indian medical thought, reaffirmed "Men ought to know that from brain only arise our pleasures, joys, laughter, jests as well as our pain, sorrow, grief and tears. That through it we think, hear, see and distinguish ugly from beautiful, the bad from good, pleasant from unpleasant. Brain makes us mad or delirious .....". Hippocrates realised that blow on one side of head occasionally is followed by convulsions or paralysis of other side of body, and he recognised the poor prognosis of patients of head injury complicated by dural lacerations. These observations made the work of Hippocrates a beacon to surgeons for over 2000 years, until the development of anaesthesia, asepsis and cerebral localization in the nineteenth century established the foundation of modern neurosurgery.

Jamieson (1976) reported that nearly all the patients sustaining head injury have persistent headaches memory difficulties and difficulties with activities of routine life, which persist for months following injury and that three months following a head injury, two thirds of the patients have still not returned to work due to sequele of brain trauma.

Rimel (1981) again documented that nearly one third of patients who had sustained minor head injuries had not returned to gainful employment after three months following head injury.

PRIMARY BRAIN INJURY

At the time of impact brain may experience linear or rotational acceleration or deceleration with respect to sagittal, lateral or vertical axis of the skull. This acceleration or deceleration may lead to contusion of brain, shearing of the axons, or tearing of bridging veins. These mechanisms are responsible for the damage the brain incurs in a closed head injury.

Contusions occur in regions where moving brain abruptly strikes the fixed skull or under areas of impact where skull is sufficiently bent inward to strike the underlying brain. These areas are marked by haemorrhage which frequently extends to pia, and by

swelling and necrosis of underlying tissue. If impact is severe, the pia will be lacerated and haemorrhage will spill out into the subarachnoid or subdural space. The neurological deficit that is produced coincides with region of direct brain injury e.g. contusion of motor strip will give rise to contralateral hemiparesis. And contusion is clinically silent when restricted to portions of brain not having clinically demonstrable function such as anterior temporal lobes or inferior aspect of frontal lobes, although this may become clinically significant days after initial injury as edema accumulates in areas where blood brain barrier has been destroyed.

Rotation of brain within the skull may result in tearing of axons within white matter, resulting in diffuse axonal injury. According to Ommaya and Ganesdly mild injuries damage only subcortical axons, but increases in rotational force will involve progressively deeper axons. There is little cerebral swelling and no increase in intracranial pressure with this form of injury.

A CT scan may demonstrate only small haemorrhage in corpus callosum and superolateral aspect of brain stem rest of the brain will appear normal though the patient may show severe neurological deficit.

A rise in intracranial pressure almost certainly occurs in humans after head injury. Children may show a rapid neurological deterioration. This is thought to be secondary to vasodilation with concomitant increased intracranial blood volume.

SECONDARY BRAIN DAMAGE

An evaluation of head trauma patients upon arrival in emergency showed that 35% have PO_2, $\angle$60 mm H_2O. 15% have systolic B.P., $\angle$95 mm Hg and 10% have a haematocrit less than 30. A head injured patient has diminution of normal protective reflexes, which may lead to obstruction of oropharynx or aspiration pneumonia. Pulmonary contusion, a flail chest or neurogenic pulmonary oedema may further compromise patients oxygenation. Hypotension is rarely a result of intracranial trauma and should alert the doctor of intra or extracorporeal haemorrhage. A positive abdominal tap is reported to occur in 17% of patients who have sustained severe head trauma.

Cerebral oedema, an enlarging haematoma or cerebrovascular engorgement may act as supratentorial mass and causes increase in intracranial pressure which produces neurological deficit by decreasing cerebral blood flow and transtentorial herniation. Enlarging

supratentorial mass is first compensated for by displacement of intracranial venous blood and CSF out of the skull. After these buffering systems are exhausted any further increase in mass will cause marked increase in intracranial pressure.

PATIENT EVALUATION

In head injured patients the initial examination must be recorded in such a way that it may be compared with subsequent examinations in order to detect a deterioration in patient's condition. Head is inspected for scalp lacerations, compound skull fractures or signs of a basilar skull fracture. In the conscious patient a detailed neurological examination should be performed with special attention to abnormalities in mental status, unilateral weakness, changes in muscle tone asymmetry of deep tendon reflexes, and presence of pathologic reflex responses. In the uncooperative stuporous patient or comatose, one must rely, upon evaluation of reflexes to detect focal abnormalities in nervous system. Special attention is paid to respiratory patterns, pupillary size and light response, oculocephalic reflex, motor response to painful stimuli and deep tendon reflexes.

An assessment of mental status is particularly difficult to record in such a way that patient's

condition can be conveyed from examiner to examiner. The Glasgow Coma scale is a standardized method of measuring the severity of patients neurological status and has a high concordance rate among different observers and should be employed in evaluating all patients of craniocerebral injury. The 15 point scale assesses patients neurologic responsiveness in three categories eye opening, verbal response and best motor response.

Many comatose patients after accident have sustained other major injuries. The surgeon must be aware of the presence of these injuries and their possible effect over brain injury.

Mild craniocerebral injuries are associated with transient vision disturbance, transient period of confusion, and a loss of memory for the moment of impact. With progressively greater degrees of brain injuries patient remains confused for proportionately longer periods of time and demonstrates a longer period of memory loss. Antegrade memory loss is loss of memory following the accident and may be the only type of memory loss in mild head injury patients. With more severe injuries the patient may demonstrate retrograde memory loss i.e. the loss of memory for events that precede the accident. With increasing degree of brain injury patient experiences the period of loss of consciousness proportional to the magnitude of injury.

The search for neurotropic drugs to reduce neurological deficits and other sequele of craniocerebral injury still continues, and in 1952 chlorpromazine was discovered, and was the first of many drugs introduced for the management of psychiatric disorders. But it was harmful rather than useful for convalescence from craniocerebral injuries because of a number of its adverse side effects. Soon other chemicals such as magnessium pemoline, methyl phenidate and PYRITINOL were discovered. Out of them only pyritinol is being increasingly used and put to research continuously. Discovered in 1957 by E Merck of Darmstadt, F.R. Germany, Since then it is in use in various neurological disorders such as sinile dementia, memory disturbances, cerebrovascular accidents organic brain syndromes and in neurosurgical disorders as sequele of craniocerebral injuries.

Darge et al (1969) subjected pyritinol in detailed investigations and drew following conclusions:

1. Pyritinol is non toxic and side effects are rare in man.
2. Minimal lethal dose was large and varied between 800-950 mg/kg in different species of animals (mouse, rat, rabbit, cat and dog), when given orally in acute toxicity studies.

3. No clinical, laboratory, histological or pathological changes were observed during the chronic studies that were performed in rats when given 100 mg/kg orally for six months.

4. Teratological abnormality in foetal development did'nt occur after pyritinol administration to rabbits in repeated oral dosage of 1000 mg/kg and in beagle dogs given 50 mg/kg daily during the entire period of pregnancy.

5. Pyritinol hydrochloride (Pyrithioxine) was absorbed very quickly when administered orally and for the most part from stomach. These studies were performed using radioactively labelled pyritinol hydrochloride using S^{35}. Maximum blood level was reached not later than 40 minutes after medication and 85% of administered dose was excreted in 12 hours. After 48 hours 94% of drug had been excreted. It may be concluded that pyritinol is completely excreted and there is no retention of active substance in body.

Ochs (1965) said that brain is almost as dependent on the glucose supplied to it as it is on the oxygen. Energy production in the brain is proved to occur by ghain of usual glucose metabolism viz. glycolysis.

Kreb's cycle, electron transport system, amino acid metabolism and G.A.B.A. shunt pathway.

Quadbeck et al (1962) performed controlled trials on rats with ^{14}C labelled glucose uptake with prior administration of pyritinol. It revealed a demonstrable increase in uptake of labelled glucose into brain even after a single dose of drug. The provision of 0.2% pyritinol in feed for 10 days enhanced the glucose uptake even more. It is noteworthy that increase in glucose was more marked in cerebram than in cerebellum and brainstem. But the findings in all three areas were statistically significant. Moreover it was found that the greater increase in ^{14}C labelled activity was located in lipoid fraction of brain but it was also observed in other structural sections of brain tissue implying its incorporation into various metabolic processes.

A disturbance of cerebral glucose metabolism has been reported to exist in a majority of patients having neurological disorders. Hoyer et al(1973) investigated such human subjects using modern scientific methods for the estimation of various parameters of oxidative cerebral metabolism such as the neuronal consumption of glucose and oxygen and the output of lactate and CO_2 both before and after the administration of pyritinol. They

conclusively proved that pyritinol elevated glucose uptake to normal values and lowered the lactate content without any change in cerebral blood flow (CBF) or oxygen consumption.

The turnover of nucleic acid and protein synthesis rise with increasing neuronal activity. RNA molecules play an important part in storage of information and its fixation on a macromolecular substrate. Kanig (1974) studied the incorporation of radioactive phosphorus into the different RNA fractions of neurons in untreated controls and under the influence of pentobarbitone and pyritinol. He observed that rate of incorporation of labelled phosphorus into massenger RNA was increased to statistically significant extent after the administration of pyritinol. It was therefore clear that pyritinol enhanced protein synthesis and facilitated various neuronal functions such as "chemical engramming" of memory.

G.A.B.A. is an important neurotransmitter which is present in brain. It is also known to possess inhibiting properties in term of neuronal dysfunction. Mori (1970) investigated the effect of pyritinol on the uptake ^{14}C labelled G.A.B.A. in mice under carefully controlled experimental conditions. Uptake of GABA was shown to be augmented to statistically significant extent after pyritinol administration.

Stoica et al (1973) working in U.S.A. injected pyritinol (8 mg/kg and 2 mg/kg) intra-arterially into baboons (Papio anubis) via vertebral and carotid arteries under controlled conditions. They demonstrated that pyritinol, when injected into vertebral arteries stimulated certain vasodilator mechanisms that exist in the brainstem resulting in a 44% increase in cerebral blood flow (CBF) and a 26% increase in cerebral oxygen consumption, whereas intracarotid administration resulted in an increase in CBF of only 11% Stoica's findings are qualitatively and quantitatively similar to the changes obtained by electrical stimulation of brainstem by Meyer and associates (1971). These workers reported that the electrical stimulation of brainstem structures produced an increase in CBF of 41% and an increase of 25% in oxygen consumption.

Awareness in its wider sense depends upon integrity of brain. Werner and his colleagues (1976) conducted autoradiographic studies on distribution of ^{3}H labelled Pyritinol in monkeys and mice. The experiments consistently showed, a much heavier radioactive labelling in cerebral cortex, hippocampus the brainstem nuclei and cerebellum then in white matter of corpus callosum, the internal and external capsules. Consciousness is a complex function of central nervous system and is measurable in E.E.G.. Certain E.E.G. patterns are

characteristic of various cerebral functional states. Increase in alertness is one effect of pyritinol which, apart from being experienced subjectively can also be recorded objectively in form of EEG. There is typical increase in frequency of cortical activity and reduction in amplitude (Desynchronization), which indicates that pyritinol facilitates arousal phenomenon in the cerebral cortex. Dolce (1970) having investigated the electrophysiological effects of pyritinol in cats, observed that it produced certain indisputable actions directly on cortical neurons, limbic system and mesencephalic reticular activating system.

The reticular activating system is of decisive importance in maintaining alertness. Consciousness is possible only if the cerebral cortex is continuously stimulated by impulses from reticular formation. This effect of reticular formation over cortex is known as Arousal and is reflected in a typical increase in frequency and reduction in amplitude of activity in EEG. The increase in alertness after pyritinol administration is seen as a distinct improvement of arousal tracings (Sierra et al, 1963).

An increase in the spontaneous electrical activity of limbic system induced by pyritinol has been observed in animals trials conducted by various

researchers such as Offenloch and Vossius (1970) who observed in cats that the spontaneous activity of neurons in the limbic system (Nucleus amygdalae) increased after infusion of PYRITINOL.

Deusinger et al (1972) showed that pyritinol improved short as well as long term memory. A four weeks double blind trial was carried out in 80 volunteers who were daily given 300 mg of pyritinol orally or a placebo. All of them underwent 7 memory tests before as well as 2 and 4 weeks after begining of medication. Results provided statistically significant improvement in performance confirming that pyritinol improved short term memory and immediate retention. A particularly interesting finding was marked improvement in performance between the second and fourth weeks which demonstrates the beneficial effects of prolonged medication with pyritinol.

Martin (1985) reported that pyritinol increases the release of acetylcholine in cerebral tissues at the synaptic level and thus improves cholinergic transmission and thus rehabilitation of cerebral function.

Learning process can be tested experimentally by conditioning animals to perform certain reflex actions. This makes it possible, for example, to measure by how much the learning time is shortened by a pharmacological

compound in question. The effect of pyritinol was tested by the following method : Rats were placed in a cage divided into two halves. Five seconds after an acoustic signal, an electric shock was applied to the half of the cage in which the rats were sitting. The test sequence was repeated at intervals of 30-50 seconds. The times required by two groups of rats (one treated with pyritinol and one control group) to develop flight reflexes to the shock free half of case were measured. In pyritinol group more rats developed a flight conditioned reflex to unpleasant stimuli more quickly than in control group (Ogawa, 1968 and Kawasaki et al, 1968).

Rossignol et al (1972) investigated the action of pyritinol, Hydergine (Codergocrine) and Vincamine in experimentally produced acute cerebral ischaemia. These workers found that pyritinol markedly accelerated the return of evoked cortical activity and distinctly. Counteracted the post anoxic increase in amplitude of thalamic evoked potentials induced by ischaemia. Similar effects but of lesser degree were observed with hydergine and Vincamine. These workers also reported that recovery after experimentally induced cerebral ischaemia was accelerated because of a protective effect of pyritinol against cerebral ischaemia.

Herrschaft (1975-78) studied the effectiveness of some 24 vasoactive drugs on cerebral blood flow (CBF)

of over 500 patients and found that the vast majority of drugs either reduced the blood flow or had no effect over it. Piracetam (1978a) and pyritinol (1978b) increased CBF of total cerebral grey matter as well as of the ischaemic grey matter. But in order to achieve this efficacy, piracetam had to be administered in a large dose of 6-10 gm intravenously as opposed to Pyritinol which was infused in a dose of 400 mg.

Kiesewetter (1984) also concluded that Drug demonstrably increased erythrocyte flexibility and blood flow. Thus microcirculation in brain is normalized and oxygen and glucose supplies are increased.

Lesney and Co-workers (1974) who were particularly active in study of clumsy children, reported their experience that hypotonia and other neurological and psychological findings in children aged 3 months to 14 years, improved after administration of encephalotropic drug i.e. pyritinol.

Declerck (1969) was one of the first to report on the use of pyritinol in successful treatment of patients with cerebral trauma. He treated 123 patients suffering from various sequele following cerebral trauma due to head injuries, with pyritinol in doses varying between 300-600 mg daily and over periods ranging from

5 to 12 weeks. He reported that symptoms such as headache, impairment of memory and concentration, mental irritability, vertigo and other such disorders were completely relieved in 85% of patients, and that 90% were able to resume gainful employment. In the control group, however, who were not treated with pyritinol, only 40% of the patients improved satisfactorily.

Gerstenbrand and his co-workers (1969) from Austria examined in detail 92 individuals who had suffered from severe head injuries. These were treated with pyritinol in daily doses ranging between 400-800 mg for periods of 2-4 weeks without any side effects being observed. As various neurological syndromes were not comparable, these workers subjected 30 patients to detailed study in three groups of 10 patients each, who were submitted to a battery of psychological tests. About one third patients in each group suffered from traumatic Apallic syndrome. The ages of all patients from group were comparable.

First group consisted of patients who had suffered from a recent brain injury and were in process of recovery.

Second group consisted of patients in whom the sequele of head injury had become stabilized. The third

group contained individuals whose symptomatology had also stabilized. The last group served as a control for the patients in the first two groups, who received PYRITINOL (500 mg) daily via oral route for four weeks. At the conclusion of study it was observed that with pyritinol there was a definite improvement in memory, concentration, visual learning ability, performance and fine motor functions. It was also reported that the drug was also effective in treating patients with frontal akinesia.

Soo Young Oh (1975) working in Switzerland, reported on 42 patients of coma who had suffered head injuries immediately prior to admission to hospital. Encephabol (PYRITINOL) was administered in doses upto 2000 mg per day. In view of nature of cerebral injury, and the condition of patients, only Encephabol was administered intravenously with I/V fluid until consciousness was regained. In the opinion of author the infusion of Encephabol produced a more rapid recovery of consciousness and reduced the time of regression of various neurological symptoms i.e. sequele of head injury.

Wild and Dolce (1976) reviewed progress in the intensive treatment of patients with severe brain damage leading to the apallic syndrome (prolonged unconsciousness akinetic mutism, coma, vigile, coma prolonge). They studied in particular, 5 adult patients for a period of

8 weeks, commencing some 6-11 weeks after the occurrence of head injury. During this total period, these subjects received Encephabol 600 mg daily, apart from other intravenous infusions and had their EEGs recorded at regular intervals. During the later recordings, Encephabol 600 mg daily was infused intravenously. Wild and Dolce concluded intensive therapy permitted recovery which was dependent on the duration of the apallic syndrome. These workers observed that oral administration of Encephabol over a long period accelerated clinical recovery in the group of patients studied .

Bystricky et al (1977) observed the effect of Encephabol after parenteral administration in 40 patients. With cerebral trauma and compared than with a control group of 40 patients. The EEG, neurological and psychological findings together with all the biochemical investigations were regularly performed in all subjects. Initially the allocation of patients to the two groups was done at random. But during latter part of study, the more severe individuals were treated with pyritinol. Initially while the patients were unconscious Encephabol was administered intravenously in doses of 600 mg daily but on recovery of consciousness the dosage decreased to 300 mg daily orally. This was continued on an average for 26 days.

According to the authors, their observations permitted the following conclusions :

1. Encephabol significantly improved the quantitative disturbance of consciousness caused by contusion.
2. It has an accelerating effect on regression of neurological symptoms.
3. Drug had a significant effect with respect to the normalization of pathological EEG findings.
4. It has a favourable effect on the restoration of intellectual function as well as on the subjective psychic condition.
5. Preparation did'nt produced any untoward side effects.

Kitamura et al (1980) reported on an intensive double blind controlled multicentre study undertaken in 270 patients who had suffered from head injuries resulting in cerebral trauma. These subjects were administered, over a period of six weeks, either Encephabol (Brand of pyritinol) 600 mg daily or a placebo of identical appearance from their findings, the authors concluded that Encephabol was significantly effective in treatment of patients recovering from sequele of cerebral trauma.

AIMS OF STUDY

AIMS OF STUDY

1. To study the role of Encephabol (PYRITINOL) in the management of craniocerebral injuries by evaluating the development and duration of various neurological sequele of craniocerebral trauma using pyritinol and compare them with control group of similar patients.
2. To categorise the patients in mild, moderate and severe degrees according to Glasgow coma scale and compare the duration and development of sequele between them.
3. To study the incidence of other injuries in patients with craniocerebral injuries.
4. To study and evaluate various other related incidences.
5. To study the role of Pyritinol over the period of recovery from unconsciousness to consciousness after head injury.

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M A T E R I A L A N D M E T H O D S

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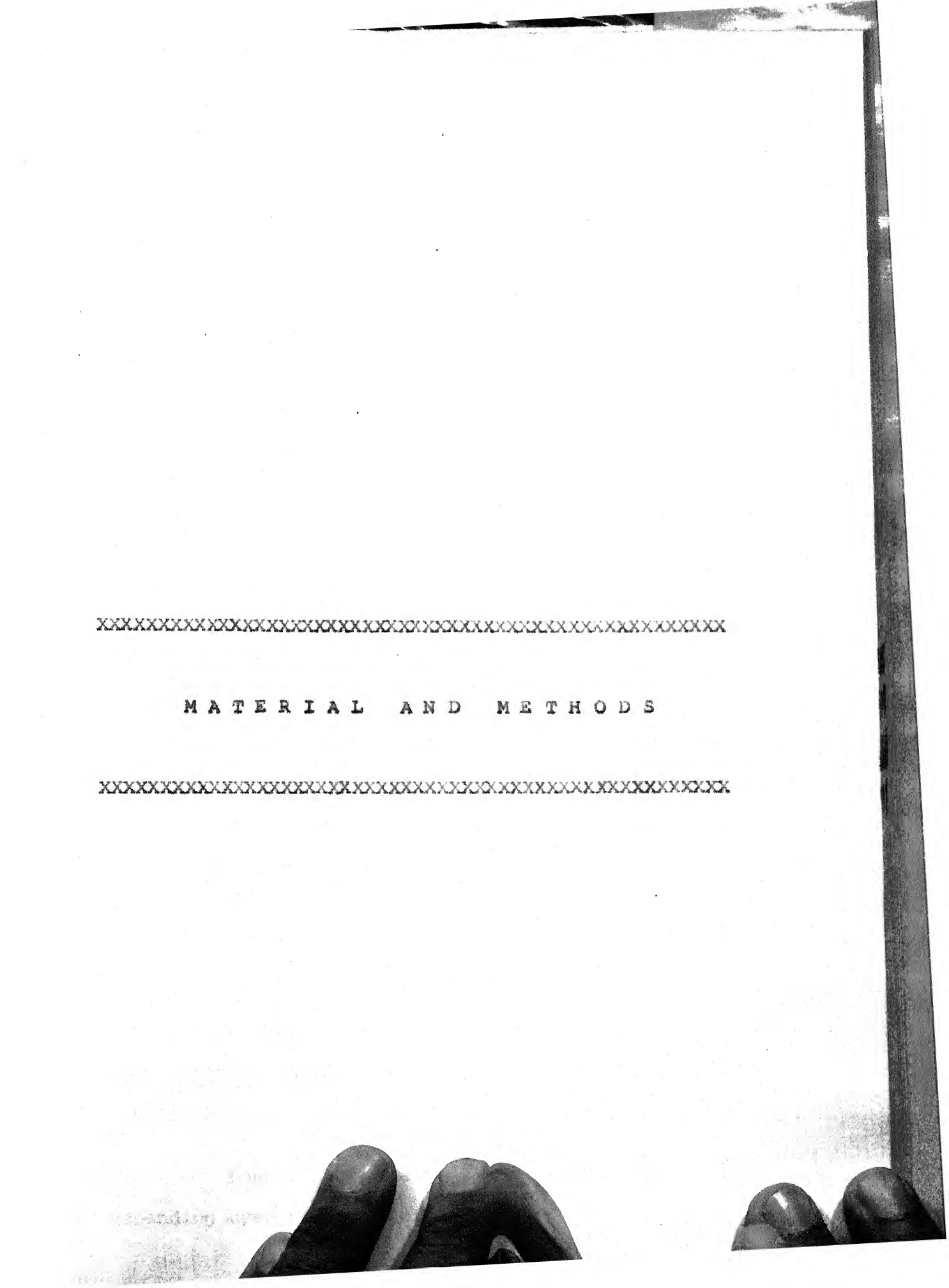


MATERIAL AND METHODS

The present study was conducted at M.L.B. Medical College, Hospital, Jhansi (U.P.). The study included a combined retrospective and prospective analyses of head injury cases admitted in this hospital from April 1989 to March, 1991.

Only those patients who had been admitted to emergency department of M.L.B. Medical College, Hospital, Jhansi as case of craniocerebral injury and had suffered certain period of unconsciousness, were taken into consideration.

Patients were divided into two broad groups :

A. STUDY GROUP : Those patients which were given PYRITINOL after sustaining craniocerebral injury for prolonged periods upto 3 months.

B. CONTROL GROUP : Those which were not given pyritinol after sustaining head injury.

Pyritinol injections, tablets and syrup were used under the brand name of "ENCEPHABOL" available in Jhansi manufactured by E. Merck of Darmstadt FR. Germany.

Dose of Encephabol was 5-15 mg/kg body weight depending upon severity of injury.

Generally 1-2 ampoules of Encephabol were administered daily but in severe cases upto 5 amploules were given daily with infusion. After recovery to consciousness patients were taken on oral dose of 1-2 tablets three times a day. Patients below 50 kg body weight were given 1 tablet (100 mg) three times daily and above 50 kg of body weight were given 1-4 tablets (Encephabol 200 mg) three times daily.

In control group the usual conventional treatment for head injury was given but in study group Encephabol was given in appropriate dosage along with conventional medical and surgical treatment of head injury.

Certain terms which have repeatedly been used in our observation are defined as under :

1. Closed head injury : is one in which scalp is intact and there is no communication between intradural contents and exterior.

2. Open head injury : implies communication between intradural contents with exterior.

3. Mild head injury : one without loss of consciousness, or only a brief period of unconsciousness with return to normal function within 24 hours and no clinical or radiological of any fractures or dural tears. Patients with Glasgow coma scale between 13-15 were kept in this group.

4. Moderate head injury : A Glasgow coma scale between 10-12 after 24 hours of head injury was considered in this group.

5. Severe head injury : Similarly a Glasgow coma scale of less than ten was considered in this group.

6. Coma : it is state of complete loss of consciousness from which a patient can't be aroused even by most powerful stimuli. Using Glasgow coma scale it is defined as "no eye opening, not obeying commands, no comprehensible verbal response.

7. Glasgow coma scale : Quantifies the severity of injury by the best response to stimuli in terms of eye opening, motor response and verbal response. Its great advantage is that it is universally accepted and observation charts based on this system allow a graphical representation of the change in neurological status the significance of which can be appreciated by all caring for the patients.

All the cases were subjected to a thorough history and examination including general, systemic and local and specific neurological examinations.

A. HISTORY

History included introduction : name, age, sex, address, ward/bed, weight, diagnosis, date of admission, date of discharge, followed by brief history with mode of

injury either hit by some automobile, fall from height (tree or roof), history of loss of consciousness, history of discharge or bleeding from natural orifices, CSF rhnorrhoea or otorrhoea, history of vomitings etc.

B. CLINICAL EXAMINATION

1. General Physical examination : Pulse, temperature, respiratory rate, blood pressure, anaemia, cyanosis, hydration etc.

2. Systemic examination : In brief examination of respiratory syste, Genito-urinary system, nervous system, cardiovascular system.

3. Specific local examination/Examination of injuries : Injuries over scalp : number, size, type, depth etc. any fractures of skull bones and other associated injuries like thoracic cage injury, bony pelvis injury, any major fracture of long bones or other bones.

4. Specific Neurological Examination : included Glasgow coma scaling. Assessed in terms of three parameters i.e. Eye opening, best motor response, verbal response, further details were discussed in working proforma viz. power in all thumbs.

5. Enquiry/Examination for specific neurological sequele of craniocerebral trauma.

- Headache : When present it was complained by patient himself. This entry did not include the post injury

infective headaches (meningitis).

- Memory losses : inability to grasp and retain images and ideas is a marked feature of acute toxic delirium, organic brain syndrome and occasionally it is a sequele of craniocerebral injury. In formulating questions on memory losses, regard was paid to patient's educational background and his/her likely personal interest.

An enquiry was made about days of week, of months (Hindi, or English), about the name of public figures whether patient is able to read the paper and to recall after a short time. Other enquiries included asking the patient to repeat seven digits forwards and five backwards.

To children and illiterate subjects some pictures of common objects were used to show them and asked after some time to recall it. For orientation and memory losses, a single enquiry common to all patients was made in addition to above tests.

The patients were asked to state the names of his/her nearest relatives, address of his home, the date of his birth, the place where he is at present time and the day of week.

IMPAIRMENT OF CONCENTRATION

It was assessed by tests of reasoning. In other

tests the patients were asked to take sevens from a hundred (i.e. 100, 93, 86, 79 .....) or the absurdities test (i.e. what would be absured if I told you I had three brothers Satish, Akhilesh and me ?

MENTAL IRRITATION

It is indicated by shouting, crying and abusing by patient or patient trying to jump in bed or grossly restless.

Every patient was asked to come to O.P.D. for follow ups for at least 3 months (12 weeks).

Every details about each patient was recorded on a standard working proforma given below :

WORKING PROFORMA

MRD No. ____

Patient's name D.O.A.

Age/Sex Ward/Bed

Weight

Diagnosis

Consultant

Brief History :

Clinical Examination :

Pulse Pupillary reaction

B.P. Plantar response

LIMB MOVEMENT

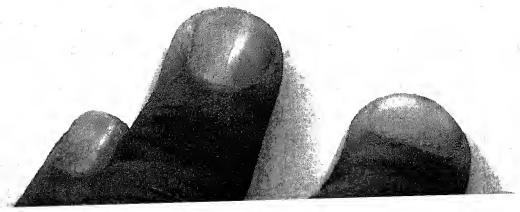
Upper Limb	Lower Limb
Normal power	Normal power
Mild weakness	Mild weakness
Severe weakness	Severe weakness
Spastic flexion	
Extension	Extension
No response	No response

Other symptoms

1. Headache
2. Memory
3. Mental irritation
4. Impairment of concentration

Date of discharge :

O B S E R V A T I O N S



OBSERVATIONS

The present study was conducted in the department of Surgery, M.L.B. Medical College, Hospital, Jhansi from March, 1990 to April, 1991. A total number of 250 patients were included in the study. Out of which, 50 died. Thus remaining 200 patients were divided into a study group of 100 patients and a control group of 100 cases too. In the present study the observations recorded were as follows :

TABLE 1 : Agewise distribution of cases.

Age groups (years)	No.of cases	Percentage
0 - 9	49	19.6
10 - 19	45	18.0
20 - 29	59	23.6
30 - 39	55	22.0
40 - 49	19	7.6
50 - 59	12	4.8
60 - 69	9	3.6
70 - 80	2	0.8
TOTAL	250	100.0

The highest incidence was reported between 20-40 years of age (20-29 years 59, 23.6% and in 30-39 years 55, 22%) i.e. 3rd to 4th decades (It may be attributable to being this age group comprised of mainly

working persons). The lowest incidence was found in old age group being only 0.8% in 70-80 years of age. This was observed that there was slight increase in incidence upto 4th decade then it started declining gradually with increasing age (Table 1).

Table 2 shows that incidence of craniocerebral injury was found more than 3 times greater in males than females. Male : female ratio being 3.17 : 1. Maximum incidence of craniocerebral injury in males was found in 20-29 years age group, because males of this age group are mostly working outside home and travel on roads on bicycle or other vehicles.

TABLE 2 : Sexwise distribution of cases.

Age groups (years)	Male		Female		Total	
	No.	Percentage	No.	Percentage	No.	Percentage
0 - 9	29	11.6	20	8.0	49	19.6
10 - 19	35	14.0	10	4.0	45	18.0
20 - 29	54	21.6	5	2.0	59	23.6
30 - 39	42	16.8	13	5.2	55	22.0
40 - 49	12	4.8	7	2.8	19	7.6
50 - 59	11	4.4	1	0.4	12	4.8
60 - 69	6	2.4	3	1.2	9	3.6
70 - 80	1	0.4	1	0.4	2	0.8
TOTAL	190	76.0	60	24.0	250	100.0

In female patients the maximum incidence was in 1st decade of life that may be attributed to playing on road and roof tops and sustaining injury in accidents and fall (Table 2).

Rural and urban incidence was found to be 1.19 : 1. Most of the cases came from rural areas (may be attributable because they have to travel from city to their villages) so they are more exposed to craniocerebral injury and road side accidents are more common on highways rather than busy city roads (Table 3).

TABLE 3 : Rural : urban distribution of cases as a whole.

Area	No.of cases	Percentage
Rural	136	54.4
Urban	114	45.6
TOTAL	250	100.0

TABLE 4 : Distribution of cases in terms of modes of injury.

Age group (years)	Mode of Injury: Fall from height		Road side accidents		Medicolegal		Total	
	No.	%	No.	%	No.	%	No.	%
0 - 15	48	19.2	26	10.4	1	0.4	75	30.0
16 - 30	10	4.0	60	24.0	20	8.0	90	36.0
31 - 45	5	2.0	43	17.2	7	2.8	55	22.0
46 - 60	3	1.2	18	7.2	3	1.2	24	9.6
7 60	1	0.4	3	1.2	2	0.8	6	2.4
TOTAL	67	26.8	150	60.0	33	13.2	250	100.0

Maximum cases fell in 16-30 years age group (90 cases). This group also contained maximum number of medicolegal cases. (Table 4).

Major cause of craniocerebral injuries in 0-15 years age group was fall from height while in all other groups road side accidents was the major cause of injury. Table 4 shows the distribution of head injury cases with respect to modes of injury.

TABLE 5 : Incidence of Open : closed head injury cases in present study.

Type of injury	No.of cases	Percentage
Open	32	12.8
Closed	218	87.2
TOTAL	250	100.0

Table 5 shows that majority of craniocerebral injuries were of closed type. Total 218 (87.2%) patients belonged to closed head injury group while only 32(12.8%) patients were in open head injury.

But severity of injury was independent of type of injury whether open or closed since many patients with open head injury were having normal or better Glasgow coma scale than those belonging to closed head injury.

Table 6 shows that the 10% of patients were having facial and skull bones fractures associated with craniocerebral injury. 15.2% of patients had upper limb

and/or thoracic cage fracture in association of cranio-cerebral injuries. 6% of patients had lower limb and/or pelvis fractures associated with craniocerebral injury and 1.2% of patients had blunt injury of abdomen(with features of peritonism) in association of head injury.

TABLE 6 : Incidence of other major injuries with craniocerebral injury.

Type of injury	No.of cases	Percentage
Face and skull bone fractures	25	10.0
Upper limb & thorax fractures	38	15.2
Lower limb & pelvis fractures	15	6.0
Blunt injury abdomen	3	1.2
TOTAL	81	32.4

TABLE 7 : Distribution of cases in terms of degree of head injury.

Degree of cranio-cerebral injury.	No.of cases	Percentage
Mild	134	53.6
Moderate	66	26.4
Severe	50	20.0
TOTAL	250	100.0

Table 7 shows that out of total 250 patients , maximum (53.6%) proportion was of mild head injuries and 26.4% patients suffered from moderate head injuries.

Remaining 20% of patients were suffering from severe head injuries. Injuries were classified according to Glasgow coma scale as under :

Milde degree : Glasgow coma scale - 13-15

Moderate degreee : Glasgow coma scale - 10-12

Severe degree : Glasgow coma scale - $\angle$ 10

TABLE 8 : Mortality in respect of various degrees of head injury.

Degree of head injury	Total No. of cases	Morta-lity	Survi-vors	Study group	Control group
Mild	134	2	132	66	66
Moderate	66	2	64	32	32
Severe	50	46	4	2	2
TOTAL	250	50	200	100	100
Percentage	100	20	80	40	40

Table 8 shows that total mortality of 50(20%) was observed out of total 250 patients. Out of these 50 mortalities, maximum cases were having severe head injury. Out of 134 patients with mild head injury tow expired. Out of 66 cases with moderate injuries 2 expired, and out of 50 severe head injury patients 46 expired.

Thus half of the patients from mild, moderate and severe head injury groups were given encephabol (study group) and half of them were not given encephabol (control group).

TABLE 9 : Incidence of post head injury headache in control group.

Severity of injury	Nil	0-1 week	1 - 2 weeks	2 - 3 weeks	3 - 4 weeks	7 4 weeks
Mild	6	33	15	11	1	-
Moderate	-	10	12	5	3	2
Severe	-	-	-	1	1	-
TOTAL	6	43	27	17	5	2
Percentage	6	43	27	17	5	2

Table 9 shows that 94% of patients of control group developed post head injury headaches of varying periods according to severity of injury. Only 6% cases did not develop any headaches. Table the distribution of cases developing post head injury headaches for various periods according to severity of head injury. There is a vague relationship in severity of head injury and duration of headache but overall most of the patients developed headache for 0-2 weeks (Table 9).

Table 10 shows that overall 34% patients of study group developed no headache at all as post head injury sequele. Only 66% patients developed post head injury headache. In mild and moderate head injuries, there was an increase in number of patients who did not develop any post injury headache. But in severe head injury no change had been observed (Table 10).

TABLE 10 : Incidence of post head injury headache in study group cases.

Severity of injury	Nil	0-1 week	1 - 2 weeks	2 - 3 weeks	3 - 4 weeks	7 4 weeks
Mild	26	25	10	5	-	-
Moderate	8	10	8	4	1	1
Severe	-	-	-	1	1	-
TOTAL	34	35	18	10	2	1
Percentage	34	35	18	10	2	1

TABLE 11 : Incidence of vertigo as sequele of head injury in control group cases.

Severity of head injury	Vertigo (weeks)					
	No vertigo	0 - 1	1 - 2	2 - 3	3 - 4	7 4
Mild	30	21	15	-	-	-
Moderate	4	16	10	-	2	-
Severe	-	-	-	2	-	-
TOTAL	34	37	25	2	2	-
Percentage	34	37	25	2	2	-

Table 11 shows that 34% patients of control group did not have any vertigo and 66% of patients developed vertigo without giving encephabol.

Table 12 shows that 44% patients of study group developed post head injury vertigo. In mild and moderate injury cases a significant increase occurred in number

of patients who did not develop any vertigo. Duration of vertigo was also lesser than control group. In cases of severe head injury both patients developed vertigo but for lesser duration.

TABLE 12 : Incidence of vertigo as a sequele of craniocerebral injury in 100 cases of study group.

Severity of head injury	No vertigo	Vertigo (weeks) 0 - 1	1 - 2	2 - 3	3 - 4	7 4
Mild	46	14	6	-	-	-
Moderate	10	14	8	-	-	-
Severe	-	-	2	-	-	-
TOTAL	56	28	16	-	-	-
Percentage						

TABLE 13 : Incidence of mental irritability after head injury in 100 cases of control group.

Severity of head injury	No irritability	Irritability (weeks) 0 - 1	1 - 2	2 - 3	3 - 4	7 4
Mild	56	7	3	-	-	-
Moderate	-	18	10	2	2	-
Severe	-	-	-	1	1	-
TOTAL	56	25	13	3	3	-
Percentage	56	25	13	3	3	-

In control group, 44% patients developed mental irritability. Out of which 25% cases had it for less

than one week interval generally 3-4 days. Only two patients had severe head injury and they had mental irritability between 2-4 weeks (Table 13).

Table 14 shows that only 34% patients of study group suffered from post head injury irritability. Out of which 21% patients showed mental irritability for 0-1 week period and only 1% cases showed it for more than 4 weeks period.

TABLE 14 : Incidence of mental irritability after head injury in 100 cases of study group.

Severity of head injury	No irritability	Irritability (weeks)				
		0 - 1	1 - 2	2 - 3	3 - 4	7 4
Mild	60	5	1	-	-	-
Moderate	6	16	8	2	-	-
Severe	-	-	-	1	-	1
TOTAL	66	21	9	3	-	1
Percentage	66	21	9	3	-	1

Table 15 depicts that 35% patients of control group exhibited impairment of concentration, in which no encephabol was given. Distribution of cases of various severity having impairment of concentration for various duration has been given in the table 15.

TABLE 15 : Incidence of impairment of concentration and memory deficit after craniocerebral injury in patients of control group.

Severity of head injury	No memory losses after recovery from injury	Weeks 0-1	1-2	2-3	3-4	7	4
Mild	50	11	5	-	-	-	
Moderate	15	13	2	2	-	-	
Severe	-	-	-	1	1	-	
TOTAL	65	24	7	3	1	-	
Percentage	65	24	7	3	1	-	

Table 16 shows that only 18 percent patients of study group exhibited impairment of concentration. In remaining 82% of cases no impairment of concentration or memory was observed.

TABLE 16 : Incidence of impairment of concentration and memory deficit after recovery from craniocerebral injury in 100 patient of study group.

Severity of head injury	No memory losses after recovery from injury	Weeks 0-1	1-2	2-3	3-4	7	4
Mild	60	6	-	-	-	-	
Moderate	22	7	3	-	-	-	
Severe	-	-	-	2	-	-	
TOTAL	82	13	3	2	-	-	
Percentage	82	13	3	2	-	-	

Table 17 shows that 50 patients of control group recovered in 1 day, 10 patients in 2 days and 6 cases in 3 days among mild head injury. Among patients with moderate head injury, 5 patients recovered in 1 day, 10 patients in 2 days, 10 patients in 3 days, 4 in 4 days and 3 patients recovered in 5 days. Patients with severe head injury recovered in 4 days and 5 days.

TABLE 17 : Period of recovery in control group.

Severity of head injury	Period of recovery(days)				
	1	2	3	4	5 or more
Mild	50	10	6	-	-
Moderate	5	10	10	4	3
Severe	-	-	-	1	1
TOTAL	55	20	16	5	4
Percentage	55	20	16	5	4

TABLE 18 : Period of recovery in study group.

Severity of head injury	Period of recovery (days)				
	1	2	3	4	5 or more
Mild	55	6	5	-	-
Moderate	9	12	9	2	-
Severe	-	-	-	1	1
TOTAL	64	18	14	3	1
Percentage	64	18	14	3	1

Table 18 shows that in study group 55 patients recovered in 1 day, 6 patients in 2 days and 5 patients recovered in 3 days among mild head injury group. In patients with moderate head injury 9 cases recovered in 1 day, 12 in 2 days, 9 patients in 3 days and 2 cases recovered in 4 days. No effect was observed in severe head injury group.

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D I S C U S S I O N

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DISCUSSION

Present study was conducted at M.L.B. Medical College, Hospital, Jhansi. Which consisted of 250 patients, out of which 50 died, so a 4-10 weeks follow up was possible for only 200 cases. Which were divided into a study group of 100 patients and given encephabol along with usual conservative treatment for craniocerebral injuries and a control group of 100 patients without Encephabol. A comparative study was carried out regarding the development of various neurological sequele after head injury and their duration, between both the groups.

Kalsbeck (1980) reported that head injuries are leading cause of death in 1-44 years age group. In present study maximum incidence was found upto 40 years of age (83.2%). It was observed that maximum incidence was in third and fourth decades mainly because this group comprised of working class of people exposed to accidents. A gradual decline was observed in incidence of head injury with advancing age after fourth decade, which may be attributed to relatively inactive and sedentary lifestyle of elderly patients.

Incidence of head injury was observed three times more prevalent in males as compared to females (M : F ratio being 3.17 : 1). The fact may be related

to the reason that males frequently go outdoor for their occupation and females do household works in our society. In females maximum incidence observed in 1st decade of life. We can ascribe it to crawling inquisitiveness of infants, experimentation of toddlers and bravado of older children as is also the case with male children.

More head injury cases were reported from rural areas than urban ones. The rural : urban ratio being 1.19 : 1. This could be related to the fact that they had to travel long distances upto city by their vehicles through highways, hence at risk for roadside accidents.

Chapman (1967) reported that accidents are more common at extremes of age i.e. childhood and old age. He also reported that principal cause of death in children in developed countries is accidents. In the present study it was observed that accidental head injury was most prevalent between 16 to 45 years age group(58%). Although children between 0 to 15 years of age were the next most prevalent (30%), elderly patients were least in number to suffer from injury i.e. 9.6% in 46-60 years age group and only 2.4% in above 60 years age group. Children mostly sustained head injuries due to fall from height. Road side accidents were principal cause of head injury in 16-45 years of age group. Medicolegal injuries were commonest in young adults i.e. 16-30 years of age.

In this study majority (87.2%) of cases were of closed head injury. Only 12.8% patients had open craniocerebral injury, but severity of injury was not directly related with type of injury. Since many patients with open head injuries were having better Glasgow coma scale than those with closed head injury.

Alan Grockard reports in Watson-Jones book of fractures and joint injuries that it is unusual for head injury to occur in isolation. Head injuries are commonestly present (80%) in road-traffic accidents alongwith other major injuries like limb fractures, fractures of pelvis and ribs. While accidents at homes i.e. in falls from height have high incidence of limb fracture whereas head is involved in only 40% of such patients. Similarly industrial accidents have highest incidence of limb fractures and only 2% of cases suffer from head injury. In present study we observed that 32.4% cases (81 out of total 250 cases) were having other major injuries along with craniocerebral injury hence majority of cases suffered isolated head injuries leaving aside other trivial injuries. 25(10%) cases suffered face and skull bone fractures all belonged to road side traffic accidents upper limb and thoracic cage fractures were found in 38 (15.2%) cases. Of these 15 cases sustained injury due to fall from height. Other in road side accidents. Lower limb and pelvis fractures were present in 15(6.0%) cases

only and in 3 (1.2%) cases blung injury abdomen was present and all these cases sustained injury in road side accidents.

Crockard HA (1981) was of the view that assessing injury severity is a major problem in management of trauma, in assessing effects of therapy. In an effort to standardize an international scale has been adopted known as GLASGOW COMA SCALE enabling one to describe the degree and types of impaired consciousness in clearly defined terms and has been used successfully in comparing treatment from one country to another. The 15 point scale assesses patient's level of consciousness in terms of three categories, eye opening, verbal response, and best motor response to external stimuli.

In the present study patients were divided into 3 categories for purpose of grouping and comparison between similar cases. The mild head injury cases (Glasgow coma scale 13-15) comprised the bulk (53.6%) of total patients while moderate head injury cases (GCS ; 10-12) comprised 26.4% and severe head injury cases (GCS ⟨10) comprised only 20% of total cases studied.

Allan H Freidman stated in Sabiston's text book of surgery that patients with mild head injuries and brief loss of consciousness are expected to make an uneventful recovery, mortality is unusual in such cases.

Patients with moderate head injury suffer a long period of post injury morbidity in form of persistent headache, memory deficits etc., but mortality is less. Severe head injury patients with a Glasgow coma scale of 9 or less exhibit a very high degree of mortality and 40% of them have a focal intracranial mass lesion and elevated reflexes can be demonstrated in approximately one third of the patients and is associated with increased mortality. According to Allan Freidman (Text book of Surgery, Sabiston, p. 1386, Vol. 2, 13th edition) mortality was found proportional to patient's age.

In the present study mortality was very low in cases of mild and moderate head injury cases. Only 2 cases out of 134 mild head injury cases and again 2 cases out of 66 moderate head injury cases died. But severe head injury cases exhibited highest rate of mortality viz. 46 patients died out of 50 patients admitted with severe head injury (92% mortality). It was also observed that no patient with a Glasgow coma scale of 8 or less remained alive. This difference in mortality between western data and our set up is probably due to limited investigative (CT scanning and neurological) facilities in our set up. In our study total 20% mortality was recorded among 250 cases studied.

Rimel (1981) documented that patients with mild head injuries suffer a surprising degree of post injury disability in the form of persistent headaches, memory deficites, impairment of concentration and difficulties with activities of daily living that persist for months following injury. He reported that one third of patients sustaining minor head injury, had not returned to gainful employment for 3 months following injury.

Declerck (1969) used pyritinol in treatment of head injuries, treating 123 patients with 300-600 daily doses of pyritinol. He observed that post head injury symptoms as headache, impairment of memory and concentration, mental irritability, vertigo and other such disorders were completely relieved in 85% and 90% patients were able to resume gainful employment, as compared to only 40% patients of control group returning to gainful employment.

In the present study 94% of total 100 patients of control group developed post head injury headache. In mild head injuries 6 patients were found not to have any post injury headache and majority of patients developed it from 0 to 7 days. Only one patient out of 66 mild head injury patients had it for 3-4 weeks. In cases of moderate head injury all patients developed headache and majority of them had it for more than one week. Only

2 cases were available of severe head injury in control group both developed headache from 2 to 4 weeks. A more than 4 weeks follow up was possible for a small number of patients.

In our study group (pyritinol given) only 66% of patients developed headaches. While 34% were free of headache out of total 100 patients. In most of the patients of mild head injury headache persisted upto one week only and in none the headache persisted for more than three weeks. More over the number of patients having headache for 2-3 weeks became only 5 with pyritinol in comparison of 11 patients without pyritinol.

In moderate head injury cases of study group, 8 patients did not develop any post injury headache, and the number of patients developing headache for more than one week reduced considerably in comparison to control group.

In severe head injury no effect of pyritinol was exhibited (Table 9 and 10).

Declerck (1969), Gerstenbrand (1969) and Bystricky et al (1977) concluded that administration of pyritinol to head injured patients effectively reduces the incidence and duration of post head injury sequele including vertigo, headache, impairment of concentration

etc. 85% of cases were completely relieved of such sequele in Declerck's experiments.

In our study 66 patients out of 100 patients of control group developed vertigo and 34% did not. In mild head injury group, 30 out of 66 patients did not have any headache while 21 patients had it for less than one week and only 15 patients had it for 1-2 weeks. No patient in this group had a persistent headache for more than two weeks.

In moderate head injury, cases of control group (No pyritinol given) 4 patients did not have any headache, 16 had it for less than one week, 10 for 1-2 weeks and only 2 patients had persistent headache for 3-4 weeks. Both the severe head injury cases had persistent headache for 2-3 weeks (Table 11).

In study group (Pyritinol was given in appropriate doses) of similar patients a considerable increase was observed in number of patients not developing any post head injury headache and hence decrease in number of patients developing post injury headache in both mild and moderate degrees of head injury. In this study group also only 2 patients of severe head injury were available and both of them developed post injury headache but for shorter duration i.e. 1-2 weeks only (Table 12).

Kitamura (1980) also studied 270 patients dividing them into study and control group, treated with pyritinol or placebo respectively and concluded that pyritinol significantly reduced post head injury neurylogical sequele. In present study out of 100 patients of control group 44% patients had post injury irritability ranging from 0-4 weeks depending upon severity of injury while 56% of cases did not had any mental irritability after regaining consciousness (Table 13).

In study group which was given pyritinol in appropriate dosage only 34% patients exhibited post head injury mental irritability. However no significant change was observed in duration of mental irritability after giving encephabol (a brand of pyritinol).

In control group of 100 patients 35 patients showed impairment of concentration and memory for varying periods, most of them upto 2nd or 3rd post injury days and a few were upto 1-2 post injury weeks. Only three patients exhibited such sequele for 2-3 post injury weeks and only one patient or severe head injury had it for more than 3 weeks. Rest of 65% patients were free of these sequele (Table 15).

In study group only 18 out of 100 patients exhibited impairment of concentration and memory deficit, and those who exhibited it after using pyritinol did so

for a shorter period than control group of similar patients.

Soo Young Oh (1975) worked on 42 patients of coma after head injury using pyritinol in high doses till the patients regained consciousness, he concluded that encephabol (pyritinol) produced a more rapid recovery of consciousness. In present study 50 cases of mild head injury from control group regained consciousness in 1 day, 10 cases in 2 days and remaining 6 cases in 3 days. While in study group which were given pyritinol 55 patients regained consciousness in just 1 day, 6 in 2 days and 5 in 3 days.

In the present study it was observed that pyritinol enhances recovery from unconsciousness to consciousness.

Patients with severe head injury did not exhibit any effect of encephabol to regain consciousness (Table 17 and 18).

Bystricky et al (1977) observed effect of pyritinol over patients of craniocerebral injuries recovering from coma and reported that the drug had no side effects.

In present study also we found no untoward side effects of the drug.

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C O N C L U S I O N

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CONCLUSION

The following conclusions were drawn from the undertaken study.

1. Head injuries are the commonest cause of death in accidents in Bundelkhand region too like in other areas where vehicles are on increase.

2. The highest incidence of craniocerebral injuries is observed between 20-40 years of age group(46%).

3. The lowest incidence of craniocerebral injuries is recorded in elderly people 60-80 years of age(4.4%).

4. Incidence of craniocerebral injuries is greater in males than females(M : F ratio being 3.17 : 1). Among males the maximum incidence is found in 20-30 years age group while in females the maximum incidence is found in first decade of life.

5. More cases come from rural areas as compared to urban areas (Rural : urban ratio being 1.19:1).

6. Major cause of head injuries in 0-15 years age group is fall from height (19.2%) commonest cause of head injuries appears to be roadside accidents (60%). Again the roadside accidents and medicolegal head injuries are commonest in 16-30 years age group.

7. Majority of head injury cases were of closed head injury. Open head injury cases constituted about (12.8%) while closed head injury are in 87.2% in present study.

8. In approximately one third patients (32.4%) head injury occurs in association of other major injuries i.e. fractures of face, skull, thoracic, pelvic or long bones. Thus majority of cases are isolated head injuries, having aside trivial injuries to other parts of body.

9. More than half (53.6%) patients sustain mild head injury, about one fourth (26.4%) sustain a moderate head injury and one fifth (20%) sustain a severe head injury.

10. Mild and moderate head injuries are associated with very low while severe head injuries are associated with very high (92%) mortality. Practically no patient survives having a Glasgow coma scoring of 8 or less after 24 hours of injury.

11. Headache is the commonest post head injury sequele (94%) incidence and duration of post head injury headache decreases (66%) after administration of Encephabol (A brand of pyritinol) in appropriate doses and is inversely proportional to degree of

head injury thus maximum in mild head injury and little in severe.

12. Next commonest sequele of craniocerebral injuries is vertigo (66%). Pyritinol decreases post head injury vertigo (44%) with maximum effect over mild, a little over severe and intermediate over moderate head injuries.

13. Slightly less common sequele is persisting mental irritability after recovery from unconsciousness (44%). Pyritinol shows a little decrease in incidence of this sequele (34%).

14. Impairment of concentration and memory deficits is least common sequele (35%) which is markedly decreased after administration of Pyritinol (18%) for long durations, with little effect over severe head injury cases.

15. Pyritinol exhibits improvement in period of recovery to consciousness in mild and moderate head injuries but no effect over severe head injury.

16. No untoward side effects are observed with treatment with pyritinol.

B I B L I O G R A P H Y

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1. Bailey and Loves : Short practice of surgery, ad. Rains and Mann, 20th edition, page 437.
2. Bystricky Z., Zoulver W. and Janik B.: Med. Welt., 643.
3. Crockard H. Alan : Head injuries, Watson Jones Fractures and joint injuries, 6th ed. page 148.
4. Darge W., Liss E., and Oeft K. : Azzneimittel-Forsch, 19 : 5; 1969.
5. Declerck A. : Acta. Neurolog et Psychiatry Belgica, 69 : 207; 1969.
6. Densinger I.M. and Haase H. : Pharmakopsychiatry, Neuropsychopharmakology, 5 : 283; 1972.
7. Dolce G. : Pharmacopsychiatry, Neuropsycho-pharmacology, 3 : 354; 1970.
8. Gerstenbrand F., Grunberger J., and Schultes H. : 2nd Danube Symposium for Neurology, Vienna, May 5-6; 1969.
9. Herrschatt H. : The effect of Pyritinol on cerebral blood flow in man. Muench. Med. Klschr, 78 : 1263; 1978.
10. Hoyer S., Oesterreich K., Weinhardt F. and Kriiger G. : J. Neurology, 210 : 227; 1975.

11. Jamieson K.G. : Epidural haematoma, Hand book of clinical neurology Vol 24, Amsterdam, North Holland Publishing Company, 1976.

12. Kanig K. : Arzneim-Forsch (Drug Research), No. 24, page 1093; 1974.

13. Kawasaki S., Kamitoshi S., Yamawaki T. and Ogawa N.: Japanese Journal of Clinics and Investigations, 45 : 196; 1968.

14. Khan M.A., Jensen K., and Krogh H.J. : Quarterly journal of studies on Alcohol, 34 : 1195; 1973.

15. Kiesewetter.H. : Concluding report on the rheological testing of encephabol and its metabolites, 1984.

16. Kitamora K., Higashi K., Nishimato A., Hori Y., Tsubokawa T., Hayakawa I., Amano K., Abe H. Ito H.: Igaku no Ayumi, 108:524;1980(English Extract available).

17. Lesney I., Rossler M., and Tokalaki L. : Cs Pediatrics, 29 : 562; 1974.

18. Martin K. : 6th International Congress of Pharmacology, Helsinki, July 20-25; 1975.

19. Martin K.J. : Effects of encephabol metabolites on choline uptake, acetylcholine synthesis and release. Research report Life Sciences, 1985.

20. Meyer JS, Terura T., and Sakamota D : Neurology (Mineap.), 21 : 247; 1971.

21. Mori A. : Shinryo (Supplement), 23 : 40; 1970.

22. Ochs S. : Elements of Neurophysiology. John Wiley and Sons. Inc., New York, 407; 1965.

23. Ofpnloch K. and Vossius G. : Naunyn - Schmiedebergs Arch. Pharmak., 266 : 415; 1970.

24. Ogawa N. : Symposium of Enbol in the field of neuropsychiatry, Osaka, 1968.

25. Oh Soo Young : Schweizreische Rundschaw Fur Medicine 64:840; 1975(English Extract available).

26. Quadbeck G., Sachsse W., Schmidt I. : Med. Exp., 7 : 144; 1962.

27. Rimel R.W., Giordani B., Barth J.T. et al : Disability caused by minor head injury. Neurosurgery, 9 : 221; 1981.

28. Rossignol P., Bouln R., Ribart M., Paultre G., Bache S., and Truelle B. : C.R. Acad. Sc. Paris, 274 : 3027; 1972.

29. Sierra G. and Reinoso-Suarez F. : Med. Exp., 9 : 84; 1963.

30. Stoica E., Meyer J.S., Kawamura Y., Hiromoto H., Hasi K., Aoyagi M., and Pascu I. : Neurology, 23 : 687; 1973.

31. Werner G., Erdmann G. and Thel S. : Arzniemittel-Forsch (Drug Research), 26 : 5; 1976.

32. Wild and Dolce G. : Journal of Neurology, 213 : 143; 1976.

33. Woelk H. : The effect of pyritinol on biosynthesis of phosphatides in the adult and age brain tissue. Abstract from lecture 14th C.I.N.P. Congress, Florence, 19th-23rd June, 1984.

S U M M A R Y

SUMMARY

The present study "EFFECT OF PYRITINOL OVER SEQUELAE OF CRANIOCEREBRAL INJURIES : A CONTROLLED COMPARATIVE STUDY" conducted at Maharani Laxmi Bai Medical College and Hospital, Jhansi, was undertaken to:

a. Study the role of Encephabol(PYRITINOL) in the management of craniocerebral injuries by evaluating the development and duration of various neurological sequele of craniocerebral trauma using pyritinol and compare them with control group of similar patients.

b. To categorise the patients in mild, moderate and severe degrees according to Glasgow coma scale and compare the duration and development of sequele between them.

c. Study the incidence of other injuries in patients with craniocerebral injuries.

d. Study and evaluate various other related incidences.

e. Study the role of Pyritinol over the period of recovery from unconsciousness to consciousness after head injury.

The following conclusions were drawn from the undertaken study.

i. Head injuries are the commonest cause of death in accidents in Bundelkhand region too like in other areas where vehicles are on increase.

ii. The highest incidence of craniocerebral injuries is observed between 20-40 years of age group(46%).

iii. The lowest incidence of craniocerebral injuries is recorded in elderly people 60-80 years of age(4.4%).

iv. Incidence of craniocerebral injuries is greater in males than females (M : F ratio being 3.17 : 1). Among males the maximum incidence is found in 20-30 years age group while in females the maximum incidence is found in first decade of life.

v. More cases come from rural areas as compared to urban areas (Rural : urban ratio being 1.19 : 1).

vi. Major cause of head injuries in 0-15 years age group is fall from height (19.2%) commonest cause of head injuries appears to be roadside accidents (60%). Again the roadside accidents and medicolegal head injuries are commonest in 16-30 years age group.

vii. Majority of head injury cases were of closed head injury. Open head injury cases constituted about 12.8% while closed head injury are in 87.2% in present study.

viii. In approximately one third patients (32.4%) head injury occurs in association of other major injuries i.e. fractures of face, skull, thoracic, pelvic or long bones. Thus majority of cases are isolated head injuries, having aside trivial injuries to other parts of body.

ix. More than half (53.6%) patients sustain mild head injury, about one fourth (26.4%) sustain a moderate head injury and one fifth (20%) sustain a severe head injury.

x. Mild and moderate head injuries are associated with very low while severe head injuries are associated with very high (92%) mortality. Practically no patient survives having a Glasgow coma scoring of 8 or less after 24 hours of injury.

xi. Headache is the commonest post head injury sequele (94%) incidence and duration of post head injury headache decreased (66%) after administration of Encephabol (A brand of pyritinol) in appropriate doses and is inversely proportional to degree of head injury thus maximum in mild head injury and little in severe.

xii. Next commonest sequele of craniocerebral injuries is vertigo (66%). Pyritinol decreases post head injury vertigo (44%) with maximum effect over mild, a little over severe and intermediate over moderate head injuries.

xiii. Slightly less common sequele is persisting mental irritability after recovery from unconsciousness (44%). Pyritinol shows a little decrease in incidence of this sequele (34%).

xiv. Impairment of concentration and memory deficits is least common sequele (35%) which is markedly decreased after administration of Pyritinol(18%) for long durations, with little effect over severe head injury cases.

xv. Pyritinol exhibits improvement in period of recovery to consciousness in mild and moderate head injuries but no effect over severe head injury.

xvi. No untoward side effects are observed with treatment with pyritinol.
